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Ottawa Hull K1A 0C9

(21) (A1) 2,111,522
(22) 1993/12/15
(43) 1994/06/17

(51) INTL.CL.[5] A01N-025/04

S.089.0/03

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Residual Antimicrobial Compositions

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(30) (US) 07/991,334 1992/12/16

(57) 1 Claim

2111522

RESIDUAL ANTIMICROBIAL COMPOSITIONS

Field of the Invention

The present invention relates to compositions having residual antimicrobial activity for use in household and institutional cleaning products and personal care products.

Background of the Invention

A variety of antimicrobial agents have been formulated into compositions that are marketed as disinfectants, cleaning products, and personal care products. However, it has been difficult to formulate antimicrobial compositions having residual activity.

Summary of the Invention

The present invention is directed to a composition having residual antimicrobial activity that comprises an aqueous dispersion of particles of at least one antimicrobial agent wherein said particles have a surface modifier adsorbed on the surface thereof in an amount sufficient to achieve a particle size of less than about 400 nanometers (nm). The compositions of the present invention can contain other conventional ingredients that are used in such compositions.

Detailed Description of the Invention

The compositions of the invention comprise antimicrobial agent containing nanoparticles. The antimicrobial agents can be any of a wide variety if compounds such as o-phenyl phenol, triclosan, p-chloro-m-zylenol, silane modified quaternary ammonium compounds, insoluble quaternary amines, and polymers complexed with phenolics or quaternary ammonium compounds.

The particles of this invention contain a discrete phase of an antimicrobial agent as described above having a surface modifier adsorbed on the surface thereof. Useful surface modifiers are believed to include those which physically adhere to the surface of the antimicrobial agent but do not chemically bond to the antimicrobial agent.

Suitable surface modifiers can preferably be selected from known organic and inorganic excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethycellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986, the disclosure of which is hereby incorporated by reference in its entirety. The

surface modifiers are commercially available and/ r can be prepared by techniques known in the art.

The surface modifier is adsorbed n tho surface of the infection control agent in an amount sufficient to maintain an effective average particle size of less than about 400 nm. The surface modifier does not chemically react with the infection control agent or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages.

As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size of less than about 400 nm" it is meant that at least 90% of the particles have a weight average particle size of less than about 400 nm when measured by the above-noted techniques. In preferred embodiments of the invention, the effective average particle size is less than about 250 nm. In some embodiments of the invention, an effective average particle size of less than about 100 nm has been achieved. With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size less than the effective average, e.g., 400 nm. In particularly preferred embodiments, essentially all of the particles have a size less than 400 nm. In some embodiments, essentially all of the particles have a size less than 250 nm.

The particles of this invention can be prepared by a method comprising the steps of dispersing an antimicrobial agent in a liquid dispersion medium and applying mechanical means in the presence of grinding

media t reduce th particle size f the infection contr l agent to an effective av rage particle size of less than about 400 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

These methods are described in detail in U.S. Patent No. 5,145,684.

The relative amount of antimicrobial agent and surface modifier can vary widely and the optimal amount of the surface modifier can depend, for example, upon the particular antimicrobial agent and surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, etc. The surface modifier preferably is present in an amount of about 0.1-10 mg per square meter surface area of the antimicrobial agent. The surface modifier can be present in an amount of 0.1-99.995%, preferably 20-60% by weight based on the total weight of the formulation.

The nanoparticles of the present invention can be incorporated into conventional disinfectant coating compositions, as for example those disclosed in U.S. Patent Nos. 4,883,828 and 5,061,485, the disclosures of which is incorporated herein.

The compositions of the present invention will incorporate an amount of one or more germicidal agents effective to both disinfect surfaces upon contact and to impart prolonged antimicrobial action to the polymeric films prepared therefrom. A wide variety of antimicrobial agents may be included in effective amounts without inducing undesirable interactions or chemical reactions between the major components of the compositions. Such agents can include chlorhexidine, chlorhexidine gluconate, glutaral, halazone, hexachlorophene, nitrofurazone, nitromersol, providone-

iodine, thimerosal, C_1-C_3 parabens, hypochlorite salts, clofucarban, clorophen, poloxameriodine, phenolics, mafenide acetate, aminacrine hydrochloride, quaternary ammonium salts, oxychlorosene, metabromsalan, merbromin, dibromsalan, blyceryl laurate, sodium and/or zinc pyrithione, (dodecyl)(diethylenediamine)glycine and/or (dodecyl)(aminopropyl)glycine and the like.

Phenolic compounds are among the preferred germicides for use in the present compositions. Useful phenolic germicides include phenol, m-cresol, o-cresol, p-cresol,o-phenyl-phenol, 4-chloro-m-cresol, chloroxylenol, 6-n-amyl-m-cresol, resorcinol, resorcinol monoacetate, p-tert-butylphenol and o-benzyl-p-chlorophenol. The biologically active, water soluble salts of these compounds may also be employed, e.g. the alkali metal salts. Of these compounds o-benzyl-p-chlorophenol is preferred due to its high germicidal power.

Quaternary ammonium salts are also preferred germicides for use in the present invention and include the N-(higher) C_{10}-C_{24} alkyl-N-benzyl-quaternary ammonium salts which comprise water solubilizing anions such as halide, e.g., chloride, bromide and iodide; sulfate, methosulfate and the like and the heterocyclic imides such as the imidazolinium salts.

For convenience, the aliphatic quaternary ammonium salts may be structurally defined as follows:

$$(R)(R_1)(R_2)(R_3)N^+X^-$$

wherein R is benzyl, or lower(alkyl) benzyl; R_1 is alkyl of 10 to 24, preferably 12 to 22 carbon atoms; R_2 is C_{10}-C_{24}-alkyl, C_1-C_4-alkyl or C_1-C_4-hydroxyalkyl, R_3 is lower alkyl or hydroxyalkyl of 1 to 4 carbon atoms and X represents an anion capable of imparting water

solubility or dispersibility including the aforementioned chloride, bromide, iodide, sulfate, and methosulfate. Particularly preferred species of these aliphatic quats include N-C_{12}-C_{18} alkyldimethylbenzylammonium chloride (myrisalkonium chloride), n-C_{12}-C_{24} alkyl-dimethyl (ethylbenzyl) ammonium chloride (quaternium 14), dimethyl(benzyl)ammonium chloride and mixtures thereof. These compounds are commercially available as the BTC series from Onyx Chemical Co., Jersey City, N.J. For example, BTC 2125M is a mixture of myrisalkonium chloride and quaternium-14.

Other useful aliphatic quaternary ammonium compounds include the N,N,-di-(higher)-C_{16}-C_{24}-alkyl-N,N-di(lower)-C_1-C_4-alkyl-quaternary ammonium salts such as distearyl(dimethyl)ammonium chloride, cetyl(-dimethyl)ethyl ammonium bromide, dicoco(dimethyl)ammonium chloride, dihydrogenated tallow(dimethyl)ammonium chloride, di-tallow(dimethyl)ammonium chloride, distearyl(dimethyl)ammonium methosulfate cetyl(trimethyl)ammonium bromide and dihydrogenated-tallow(dimethyl)ammonium methosulfates.

Other useful nitrogenous germicides include benzethonium chloride, cetylpyridinium chloride, methyl-benzethonnium chloride, domiphen bromide, gentian violet, and the like.

The total concentration of the germicidal component of the present liquid compositions can vary widely, depending upon its antimicrobial activity, solubility, stability and the like. The present disinfectant compositions will preferably comprise about 0.01-10%, most preferably about 0.05-5% by weight of the phelonic or quaternary ammonium salts based on the disinfectant polymeric composition as a whole. Highly

durable abrasion resistant films can be achieved when the total concentration of the germicidal agent in the present compositions comprises about 0.01%-50%, preferably about 0.25-20%, and most preferably about 0.5-15% by weight based on the weight of the dissolved copolymers.

The disinfectant compositions are liquids which are applied to the surfaces to be treated by dipping, spraying, brushing, roller coating, pad coating or using similar coating procedures. For household applications, hand-operated pump-type or pressurized aerosol sprayers can be effective. Although the present compositions are particularly adapted to adhere to hard surfaces, they can also be employed to coat or otherwise treat materials such as sponges, flexible plastics, textiles, wood and the like. Generally, the coating process is continued to the extent required to deliver an amount of the liquid composition which rapidly dries to a clear, uniform polymeric film under ambient conditions, e.g., about 50-100 mg/in^2 of liquid composition is generally effective to disinfect and impart prolonged antimicrobial protection to tile surfaces.

The nanoparticles, when incorporated into the cleaning product, would adhere to the surface (due to their small size or by suitable coating on the particle or both).

By adhering into the cracks and crevices of the appropriate surfaces, the nanoparticles could offer residual antimicrobial activity that could not be obtained by other means.

The compositions of the present invention provide advantages over conventional such compositions since suitable antimicrobials would not have to be entrapped or bound to a polymer eliminating the hazard

associated with unreacted monomers or initiators. The nanoparticles incorporated in these compositions are smaller particles that allow for better coverage of the substrate providing a greater protective barrier. Furthermore, these compositions are more easily dispersed in aqueous medium and provide improved and efficient delivery of products through spray apparatus.

The compositions of the present invention can be illustrated by the following representative example.

Example 1

Antimicrobial Hand Soap

	Wt. %
Olefin Sulfonate	30.0
Cocamide DEA	1.0
Cocamidopropyl Betaine	5.0
Nanoparticle Antimicrobial (PCMX)	1.0
Sodium chloride	0.5 - 2.0
Citric acid to desired pH	
water	61.0 - 62.5

Example 2

Residual Antimicrobial Formulation

	Wt. %
Water	0.5 - 100
Solvent	5 - 60
Surfactant	1 - 8
Residual Antimicrobial nanoparticle	0.1 - 1.0

The foregoing specification, including the specific embodiments and examples is intended to be illustrative of the present invention and is not to be taken as limiting. Numerous other variations and

We Claim:

1. A composition having residual antimicrobial activity comprising an aqueous dispersion of particles of at least one antimicrobial agent wherein said particles have a surface modifier adsorbed on the surface thereof in an amount sufficient to achieve a particle size of less than about 400 nanometers (nm).

ABSTRACT

The present invention is directed to a composition having residual antimicrobial activity comprising an aqueous dispersion of particles of at least one antimicrobial agent wherein said particles have a surface modifier adsorbed on the surface thereof in an amount sufficient to achieve a particle size of less than about 400 nanometers (nm). The compositions of the present invention can contain other conventional ingredients.